Equilibrium Solubility
In
Simulated Intestinal Media

Orbito Team – Strathclyde University
WP 1
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Work Package 1

• Task 1.1 Design of Experiment
• Task 1.3 Design and characterisation of a set of SGIM reflecting the compositions of human GI fluids in the fasted and fed states
• Task 1.4 Optimisation and validation of novel small scale models for dissolution rate and apparent solubility in the designed SGIM
• Task 1.11 Determination of excipient effects on API behaviour in developed in vitro models
Coverage

• Media Parameters
• Basic Experimental Protocol
• Design of Experiment Studies
• Four Component Mixture Design Studies
  – Intestinal Solubility Topography
• Practical Application
  – BCS, Intestinal Solubility Window, PK Prediction
• Experimental Caveats
• Conclusions
Media Parameters

**Equilibrium Solubility Measurement**

1. pH adjusted & sample placed in shaker for one hour.
2. 1 ml transferred to Eppendorf tube.
3. Drug added.
4. Transferred to centrifuged tube.

- Bile salts
- Monoglyceride
- Lecithin

**Chart**

1: Carvedilol
2: Tadalafil
3: Albendazole
4: Bromocriptine
5: Valsartan
6: Indomethacin
7: Ibuprofen
8: Aprepitant
9: Felodipine
10: Zafirlukast
11: Itraconazole
12: Fenofibrate
13: Probucol

## Media Parameters - Design of Experiment

- **Fasted**
  - Fractional factorial design (quarter)
  - 7 parameters
  - 66 experiments (including duplicates)
- **Fed**
  - D-optimal design
  - 8 parameters
  - 94 experiments (including duplicates)

<table>
<thead>
<tr>
<th>Parameter/Ingredient</th>
<th>Substance</th>
<th>Fasted</th>
<th>Fed</th>
<th>Full Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower Limit</td>
<td>Upper limit</td>
<td>Lower Limit</td>
<td>Upper Limit</td>
</tr>
<tr>
<td>Bile salt (mM)</td>
<td>Sodium TC</td>
<td>1.5</td>
<td>5.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Lecithin (mM)</td>
<td>Egg PL</td>
<td>0.2</td>
<td>0.75</td>
<td>0.5</td>
</tr>
<tr>
<td>Buffer (mM)</td>
<td>NaH2PO4</td>
<td>15</td>
<td>45</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Maleic acid</td>
<td>-</td>
<td>-</td>
<td>28.6</td>
</tr>
<tr>
<td>Salt (mM)</td>
<td>NaCl</td>
<td>68</td>
<td>106</td>
<td>125</td>
</tr>
<tr>
<td>pH</td>
<td>NaOH/HCl</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Enzyme (U/ml)¹</td>
<td>Pancreatin</td>
<td>0.5</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Fatty acid (mM)</td>
<td>Sodium oleate</td>
<td>0.5</td>
<td>10</td>
<td>0.8</td>
</tr>
<tr>
<td>Monoglyceride (mM)</td>
<td>Glyceryl Monoleate</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Note:
- ¹ Enzyme activity expressed as units per milliliter.
Fasted - Design of Experiment


Unpublished Data
Multiple – Design of Experiment Systems

- Fasted
- Fed
- Combined
- Dual range
- 9 point Fasted and Fed


9 Point – unpublished data
# Impact DoE Design on Factor Significance

<table>
<thead>
<tr>
<th></th>
<th>Fasted</th>
<th>Fed</th>
<th>Dual Level – Fasted</th>
<th>Dual Level – Fed</th>
<th>9DOE Fasted</th>
<th>9DOE Fed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indomethacin</strong></td>
<td>pH Bile Salt Buffer Oleate</td>
<td>pH Bile Salt Oleate</td>
<td>pH</td>
<td>pH</td>
<td>pH</td>
<td>pH</td>
</tr>
<tr>
<td><strong>Aprepitant</strong></td>
<td>Oleate pH Lecithin</td>
<td>Oleate Bile Salt pH</td>
<td>Oleate Lecithin MG</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Tadalafil</strong></td>
<td>Bile Salt pH Buffer Lecithin Oleate Salt</td>
<td>Bile Salt Oleate</td>
<td>NS</td>
<td>NS</td>
<td>pH</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Zafirlukast</strong></td>
<td>pH Oleate Bile Salt Lecithin</td>
<td>pH Bile Salt Oleate</td>
<td>pH Cholesterol MG</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Carvedilol</strong></td>
<td>Bile Salt Oleate</td>
<td>Bile Salt pH Buffer Oleate</td>
<td>NS</td>
<td>NS</td>
<td>Bile Salt pH</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Felodipine</strong></td>
<td>pH Oleate Lecithin Bile Salt Lecithin</td>
<td>Oleate Bile Salt pH Lecithin</td>
<td>pH Oleate Lecithin MG</td>
<td>Oleate Lecithin Bile Salt MG</td>
<td>Oleate</td>
<td>Bile Salt</td>
</tr>
<tr>
<td><strong>Probucol</strong></td>
<td>pH Oleate</td>
<td>Bile Salt MG Oleate Lecithin pH</td>
<td>Oleate BS:PL</td>
<td>Oleate</td>
<td>pH</td>
<td>NS</td>
</tr>
</tbody>
</table>

Smaller Design = Lower Factor Resolution
Four Component Mixture Design (4CMD)

- DoE – indicates drug specific behaviour
  Difficult to visualise
- Four components
  Bile salt
  Sodium oleate
  Lecithin
  Glyceryl monooleate
- Total amphiphile concentration
  11.7 mM
- pH 7.4

Tetrahedron of solubility
Each Triangle – Ternary Phase Diagram
4CMD pH 7.4 TAC 11.7 mM

Aprepitant  Carvedilol  Zafirlukast

Fenofibrate  Felodipine  Spironolactone

4CMD Matrix

- Indomethacin

Unpublished Data
Relationship with DoE

• Indomethacin
Practical Application - BCS & DCS

Indomethacin

Dose / Solubility Ratio

Class I

Class II

Class III

Class IV

Effective permeability (cm/s x 10^-4)

Felodipine

Dose / Solubility Ratio

Class I

Class II

Class III

Class IV

Effective permeability (cm/s x 10^-4)
Practical Application - Compartmental Analysis

- 4CMD represents 9 possible intestinal compartments

![Indomethacin Solubility](image1)

![Fenofibrate Solubility](image2)

Unpublished Data
Practical Application – Prediction

**Solubility**

- **Overall Solubility**
- **Fasted Solubility**

**Pharmacokinetics**

Unpublished Data

- Indomethacin (a)
- Carvedilol (b)
Experimental Caveats – Factor Concentrations


Experimental Caveats – Factor Ratios

- 4CMD Amphiphile number & amphiphile ratio

Unpublished Data

Fenofibrate
Conclusions

• Single media composition solubility measurement (SIF or HIF)– limited value
  – Position within topography unknown, variability unknown
• Increase number of measurement points – increased information
  – Big DoE – factor and solubility range information
  – Wee DoE – solubility range – with caveats – limited or no factor information
• Choice of media components – the greater the better – see below
  – Number, Concentration and Ratio – appropriate
• Beware – drug specific behavior

• Improved statistical information – HIF composition and SIF solubility
• Structured solubility behavior is present
• Solubility prediction – looking possible – limited initially
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